Buchanan Ingersoll
ATTORNEYS

1776 K Street, N W
Suite 800
Washington, DC 20006-2365

T 202 452 7900
F 202 452 7989
www buchananingersoll com

Edward John Allera
(202) 452-7985
alleraej@bipc.com
Theodore Sullivan
(202) 452-7992
sullivantm@bipc.com

April 19, 2005

Confidential
Attorney-Client Privilege

HAND DELIVERY - RETURN RECEIPT REQUESTED

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Subject: **Docket No. 2004P-0068 - Additional Information and Statement in Support of the Citizen Petition filed by Ferring Pharmaceuticals Inc.**

Dear Sir or Madam:

Because the principle use of desmopressin acetate (DDAVP®) is in a sensitive pediatric population, and because the drug is the first and only oral peptide approved under a New Drug Application, it is critical that the Food and Drug Administration carefully consider all the relevant factors that impact the safety and effectiveness of any generic oral desmopressin drug product. The above cited Citizen Petition filed by Ferring Pharmaceuticals Inc. (Ferring), discusses these factors, and it provides some recommendations as to the data that are necessary to demonstrate that two oral desmopressin drug products are bioequivalent.

The March 8, 2005 letter, filed on behalf of Barr Laboratories, Inc., in response to the Citizen Petition, raises two primary issues in support of its position that traditional pharmacokinetic studies are sufficient to demonstrate bioequivalence for desmopressin. First, the letter contends that current bioanalytical methods are sufficient, despite desmopressin's low absorption, low blood plasma levels, and pharmacological activity at levels below the quantification capacity for accepted analytical methods. Second, Barr states that conventional bioavailability studies in healthy adults are a sufficient surrogate for the enuretic pediatric patients, who are the intended target population for the drug.

2004P-0068 SUP 1

As will be discussed in detail in the follow-up submission, Barr's position is in error both medically and legally. Desmopressin presents unique bioequivalence issues, and no approval should be granted for a generic oral desmopressin until the following data have been gathered and analyzed.

(1) Evidence from appropriately designed comparative clinical studies demonstrating bioequivalence to desmopressin in terms of both pharmacokinetic and pharmacodynamic properties including intrasubject as well as intersubject variability in adsorption **and** duration of action as determined by measurement of urine osmolarity and flow rates in water loaded enuretic children;

(2) Separate bioequivalence evidence for each dose level, due to the lack of dose proportionality between strengths in the RLD; or

(3) If bioequivalence is not established by the above specified pharmacokinetic and pharmacodynamic studies in enuretic children, ANDAs for products containing desmopressin must provide evidence from appropriately designed and validated comparative clinical trials demonstrating efficacy and safety equivalent to RLD in this target population.

As further support for the seriousness of the medical issues, enclosed are an original and three copies of an expert statement in support of the Citizen Petition regarding the bioequivalence issues with desmopressin. This expert statement provides the opinion of Dr. Jose Cara, a clinician with significant experience in treating pediatric enuresis patients. Ferring anticipates filing additional, more detailed, comments on the Barr letter in approximately two weeks.

Respectfully submitted,

Edward John Allera
Theodore M. Sullivan

Children's Hospital
of Michigan
Detroit Medical Center / Wayne State University

The Carman and Ann Adams
Department of Pediatrics
Division of
Pediatric Endocrinology

3901 Beaubien
Detroit, MI 48201-2119
313-745-5532 Phone
313-745-0256 Fax

Desmopressin Bioequivalence

Jose F. Cara, M.D.
Associate Professor
Department of Pediatrics
Wayne State University School of Medicine
Division Head
Pediatric Endocrinology and Diabetes
Children's Hospital of Michigan/Henry Ford Health System

January 10, 2004

José F. Cara, M.D.

January 10, 2005
Date

Children's Hospital
of Michigan
Detroit Medical Center / Wayne State University

The Carman and Ann Adams
Department of Pediatrics
Division of
Pediatric Endocrinology

3901 Beaubien
Detroit, MI 48201-2119
313-745-5532 Phone
313-745-0256 Fax

I. INTRODUCTION

1. I have been requested by Ferring Pharmaceuticals, Inc. ("Ferring") to review a Citizen Petition which was filed on its behalf, requesting that the Commissioner of Food and Drugs establish specific bioequivalence requirements for oral products containing desmopressin (also referred to as DDAVP), because of several unique aspects of the drug.

2. In this regard, I reviewed the citizen Petition as well as the literature on DDAVP and other hormone based drug products.

3. I am quite familiar with desmopressin and have used it extensively in my practice. I am Division Head of Pediatric Endocrinology and Diabetes at the Children's Hospital of Michigan. I trained as a Resident in Pediatrics at Maimonedes Medical Center in Brooklyn, New York, and at the State University of New York Health Science Center, Syracuse, New York. I was also a Fellow in Pediatric Endocrinology and Diabetes at the Children's Hospital of Philadelphia, Pennsylvania.

4. My areas of interest and study have been pediatrics and pediatric endocrinology, with special emphasis on insulin and insulin like growth factor (IGF) biochemistry and physiology, including hormone receptor interactions, insulin resistance and sensitivity, and ovarian functions of insulin and the IGFs.

5. In recent years my interests have focused more on clinical practice and clinical research rather than bench research. Some areas that fall under my responsibility as division head include: overseeing our divisions teaching of residents and medical students; developing and implementing guidelines for the diagnosis and treatment of endocrine disorders and diabetes, including hypocalcemia, hypoglycemia, intrauterine growth retardation, growth hormone-related disorders, hypothyroidism, metabolic disorders, endocrine malignancies, and reproductive disorders; and monitoring the quality assurance activities of our division.

II. EXPERIENCE WITH THE USE OF DESMOPRESSIN

6. Desmopressin is indicated for the treatment of primary nocturnal enuresis in children six years of age and older and for the treatment of central diabetes insipidus in children four years of age and older. I have treated hundreds of children and adults with those conditions.

7. I concur with the Petition that desmopressin has very high potency and that there is a relative insensitivity of existing assays for the drug, which limits the ability of pharmacokinetic data to predict bio-potency, duration of action and other clinical parameters necessary for the clinical care of patients. With diabetes insipidus, the efficacy of desmopressin is best determined by the observed clinical response, as blood levels do not directly correlate to the drug's clinical anti-diuretic effect. Thus, for a new generic desmopressin coming on the market, I would want to be able to evaluate pharmacodynamic data for the product, especially compared with other already marketed oral desmopressin drug products, in order to have a better understanding of its likely clinical effect. In this regard, as a clinician, I would like to be able to ascertain the expected biological response, anti-diuretic activity, and length of action. Duration of action is

particularly important, as dosing above the minimum effective dose does not particularly affect the degree of anti-diuresis but results in extended duration of action.

8. I also agree with the Petition that, because of very low oral absorption and perhaps other factors, there are very significant intrasubject and intersubject variations in bioavailability and biopotency.

9. I further agree with the Petition's statement that traditional bioequivalence measurements are not appropriate in the case of desmopressin because of the lack of dose proportionality of the drug. In my clinical experience the lack of dose proportionality and the intersubject variability cannot be resolved by simply reducing the dose. While this may reduce the likelihood of hyponatremia, it is likely to impact drug efficacy.

10. In my clinical practice, I accept the intersubject variability of DDAVP and begin treatment with a dose that appears reasonable based on the age, size and weight of the patient. I observe closely the clinical response and adjust the dose and the dosing interval based on these observations. Dose individualization is necessary for each and every patient and is, in part, determined by the patient's age, size, medical history and other factors. Dosing in children is particularly difficult as it is not proportional, based on weight, to the adult dose. The typical pediatric dose is between 25 and 100 percent of the adult dose.

11. In my experience, pediatric patients are more sensitive to the side effects of DDAVP. In particular, pediatric subjects, with their higher volume to weight ratio, are far more susceptible to fluid shifts than larger, adult subjects, and run a greater risk of hyponatremia.

III. THE PROBLEMS OF GENERIC DESMOPRESSIN

12. There appears to be significant variation in absorption and drug effect when dosing at a fed versus fasting state.

13. Dose proportionality is lacking with DDAVP. For example, the 0.1 mg dose is not proportional to the 0.2 mg dose (i.e., two of the 0.1 mg tablets do not give the same effect as one 0.2 mg tablet.

14. As indicated above (see Paragraph 7), the duration of the effect of DDAVP is clinically more important than the level of effect of the drug. Maximal blood levels, and maximal biological response, are less important than the length of time that the effective dose remains in bloodstream and is biologically active. This again is consistent with the opinion that pharmacodynamic data, such as duration of clinical effect, is more important than pharmacokinetic data.

15. DDAVP is prescribed for a wide variety of patients with a wide range of medical disorders and with a broad range in age, from newborn to elderly. The effective dose, the duration of effect, and the susceptibility to side effects varies greatly in these patients, and must be taken into consideration when reviewing the data for any generic DDAVP product, if such product is to be pharmaceutically equivalent.

16. For the foregoing reasons, I would be very hesitant and unlikely to switch from a branded desmopressin to a generic counterpart, unless I had knowledge of the latter's clinical activity profile compared to the branded drug. Because of the potential risks, I would not assume that generic desmopressin and the generic product were biologically equivalent to one another and simply prescribe the generic drug. Rather, I would order the patient to take the branded desmopressin by writing "dispense as written" on the prescription.

17. In summary, based on my clinical experience, any generic desmopressin submitted for review by FDA should be required to: (1) perform studies demonstrating pharmacokinetic and pharmacodynamic equivalence; (2) perform separate bioequivalence studies for each dose; or (3), in the alternative, perform safety and efficacy studies. Additionally, these studies should evaluate the pharmacokinetic and pharmacodynamic relationships in various age groups, include comparative pharmacodynamic dosing studies, and, in general, not rely solely upon pharmacokinetic data.

José F. Cara, M.D.

January 10, 2005
Date